Docket No.: CBR 3.0-017 CONT
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Moo-Young et al.

Application No.: 10/736,428 Confirmation No.: @@@

Filed: December 15, 2003 Art Unit: 1617

For: TRANSDERMAL ADMINISTRATION OF MENT Examiner: L. Q. Wells

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF YUN-YEN TSONG UNDER 37 C.F.R. § 1.132

Dear Sir:

I, Yun-Yen Tsong, am a citizen of the United States, residing at 33 Evergreen Drive, North Caldwell, New Jersey 07006.

1. I received a Bachelor's of Science degree in Pharmacy from National Taiwan University, Taipei, Taiwan in 1960, and a Doctorate in Biochemistry from the University of Wisconsin, Madison, Wisconsin, in 1969. I have received two U.S. patents, and have authored 39 publications in peer reviewed scientific journals, as well as 37 published and presented abstracts in scientific meeting proceedings. I am a Registered Pharmacist in the State of New York (since 1977). I am also a member of the following professional societies: American Chemical Society, Endocrine Society, American Society for Reproductive Medicine, American Association of Pharmaceutical Scientist Controlled Release Society, New York Academy of Science, and American Society for the Advancement of Science.

2. I was employed as a Senior Medicinal Chemist by Smith Kline and French Laboratories, Philadelphia, Pennsylvania, from 1968 to 1970; and from 1970 to the present, I have been employed by the Center for Biomedical Research, Population Council, New York, New York, as a Research Associate from 1970 to 1972, as a Scientist from 1973 to 1996, and as a Senior Scientist from 1997 to the present date.

3. I am familiar with the prosecution of the above-identified pending U.S. Patent Application No. 10/736,428, as well as that of its parent Application No. 09/154,287 in the U.S. Patent and Trademark Office, and in fact participated in an interview with the Examiner on January 14, 2005, at the U.S. Patent and Trademark Office attended by the Examiner, myself, Arnold H. Krumholz, attorney of record, and Mr. Albert Radlmaier, and Dr. Thomas Heiner. At that personal interview, the references of record were discussed, as were the latest outstanding rejections in this case, which included a discussion of the Official Action of July 23, 2004, and the rejection of the claims as being unpatentable over Herschler, U.S. Patent No. 4,177,267, in combination with Bardin *et al.*, U.S. Patent No. 5,342,834.

4. In particular, during the aforementioned personal interview, the Examiner requested a direct comparison with the specific non-5α-reducible, 7α-modified androgens of the present claims substituted in the precise formulations utilized in Example 11 of Herschler *et al.*, at the preferred level of 3% androgen. This was intended to represent a direct comparison between the present invention and the precise 17α-ethyl-19-nortestosterone preferred by Herschler *et al.*, in the preferred compositions of Herschler *et al.*

5. In order to comply with the Examiner's request, specific tests were carried out under my direct supervision and

control in order to compare the flux rate of 7α-methyl-19-nortestosterone (MENT) with that of the 17α-ethyl-19-nortestosterone of Herschler *et al.*, which is a 5α-reducible androgen. Identical cream formulations were prepared using the formulations in Example 11 including MENT, on the one hand, and 17α-ethyl-19-nortestosterone, on the other. Each of these formulations thus specifically included the required amounts of cetyl alcohol, stearyl alcohol, polysorbate 80, water, and dimethylsulfoxide, along with 3% of the steroid in each of the formulations in question. The flux rate of these cream compositions through rat skin sandwiched between two chambers of a modified Franz cell was carried out to determine the flux rate of these two steroids through skin. The skin of a male Sprague Dawley rat (200-250 grams body weight) was used for this study. Each of the test creams was placed on the rat skin in the upper chamber, and the lower receptor chamber was filled with an isotonic saline solution (7 mL) under constant stirring. The saline solution was kept at 37°C using a water jacket. A 200 μL sample of saline was withdrawn from the lower chamber at hourly intervals and the concentration of the particular steroid (MENT) and 17α-ethyl-19-nortestosterone was determined using HPLC. Attached hereto as Figure 1 are the results obtained, which establish that the MENT had a very high *in vitro* flux rate as compared to the 17α-ethyl-19-nortestosterone. Each of the steroids was tested on 20 such skins, and the statistical analysis by Paired t test of the results indicated that in each hourly interval over the four-hour period the MENT had a significantly higher flux rate than the 17α-ethyl-19-nortestosterone.

6. These results in fact confirm the results which I obtained in my previous declaration, and which are also set forth in the specification of the patent application in

question. The results are believed to clearly establish that the non-5α-reducible, 7α-modified androgens of the present claims are unexpectedly superior, in direct tests with the closest available prior art, and demonstrate unexpectedly superior results in connection with the flux rate thereof.

7. It is again for these reasons that I remain of the opinion that use of transdermal dosage forms of non-5α-reducible, 7α-modified androgens, such as MENT, in transdermal dosage forms with the capability of delivering between about 400 and 1600 micrograms of the androgen in bioavailable form over a 24-hour period, and/or containing at least 2 mg of the androgen in the transdermal dosage form, is unobvious in light of the references relied upon by the Examiner, including Herschler and Bardin *et al*.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 6/1/05

YUN-YEN TSONG

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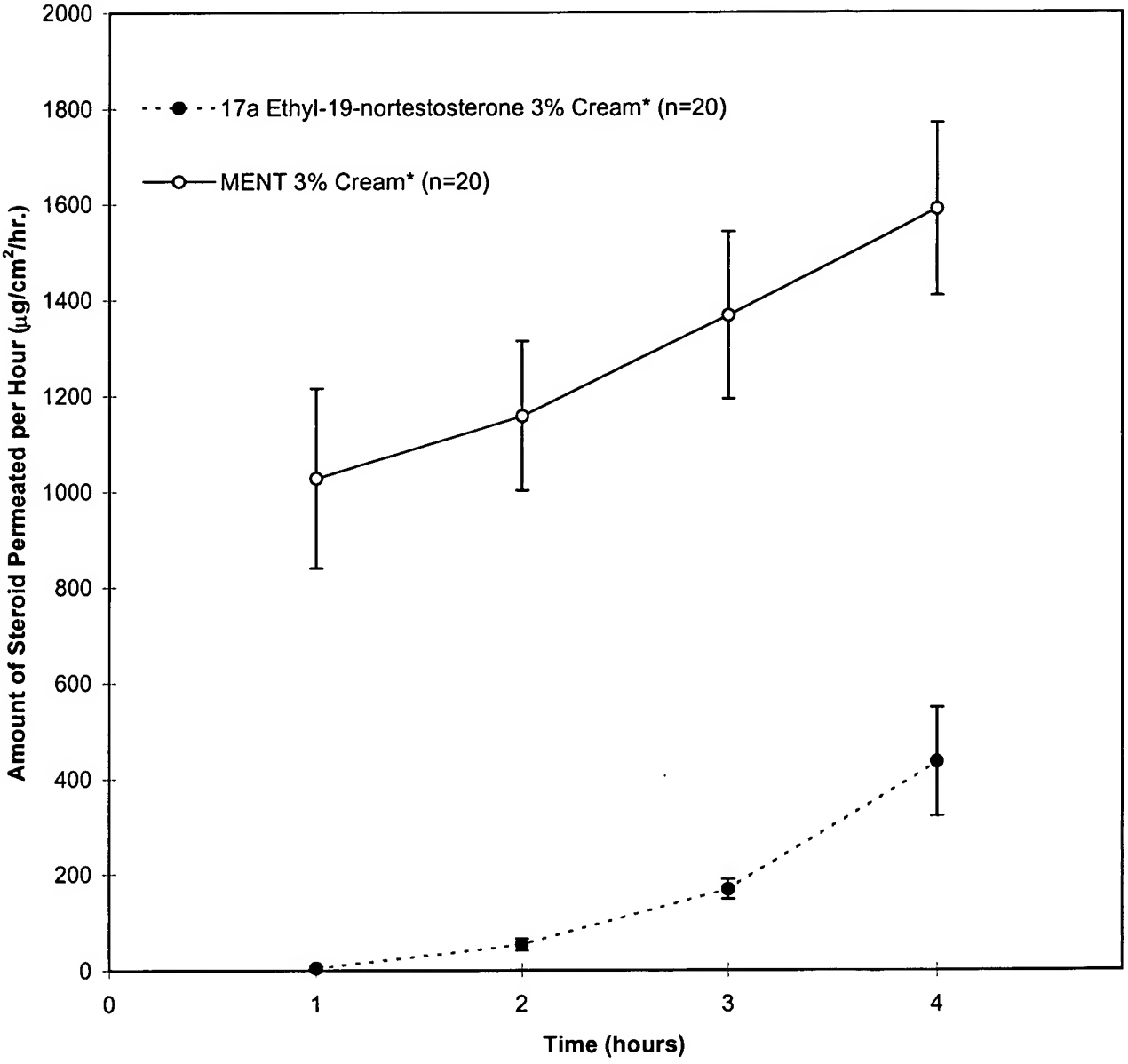
Figure 1
Permeation Profile (Flux Rate) of MENT and 17α Ethyl-19-nortestosterone Across Rat Skin



* Creams were prepared according to example 11, Herschler. US Patent 4,177,267

Paired t test:
1 Hour: $p<0.0000278$
2 Hour: $p<0.000000747$
3 Hour: $p<0.000000914$
4 Hour: $p<0.00000452$